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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,103	12/10/2001	Anthony Boey	20801-000810	3038

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	**PAPER NUMBER**
1615	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/744,103	BOEY ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 1-25-07 is acknowledged.

Claims included in the prosecution are 1-66.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

2. Claims 1-8, 12-13, 15-17, 21-22, 32-39, 43-45, 49, 55, 57 and 59 are rejected under 35 U.S.C. 102(a) as being anticipated by Lee (5,908,777).

Lee discloses compositions containing condensed nucleic acid preparations encapsulated within the liposomes for transfection. The liposomes contain DOPE/PS and PEG-PE. The condensing agent is polylysine, protamine or spermine or spermidine. (abstract, col. 5, line 23 through col. 7, line 64 and examples, Example 1 in particular). The sizes of the liposomes as observed in Fig.3 ranges from 100-200 nm. Although Lee does not specifically state the molecular weight of PEG, PEG-lipid complex in Lee is prepared according to the method of by Lee's previous work wherein PEG 2000 was used.

The examiner has already cited Lee BBA 1995 of interest in this context (note materials section).

Applicant's arguments are once again based on Dr. Mac Lachlan's declaration. These arguments have been have been fully addressed before. As pointed out before, Dr. Mac Lachlan argues the following way: "Lee et al. discloses nucleic acid-lipid complexes comprising anionic liposomes (see, col. 8, lines 7-9) and nucleic acid-polylysine-complexes (see, col. 8, 1ines23-24). Only after the liposomes are fully formed are they mixed with nucleic acid-polylysine complexes (see, e.g., col. 8, lines 27-29) in deionized water. Lee et al. characterizes the interaction between the fully formed liposomes and nucleic acid-polylysine complexes in the liposomes as encapsulation of the nucleic acid-polylysine complex. However, given that DNA does not readily cross lipid membranes, one of skill in the art would appreciate that mixing of a nucleic acid-polylysine complex with preformed liposomes in an aqueous solution does not result in entrapment of DNA within the internal space of the liposomes, but would, instead, result in formation of nucleic acid-lipid complexes. Without a step that destabilizes the liposome membrane, the nucleic acid would not be able to enter the liposome and be encapsulated. Thus, in contrast to the presently claimed liposomes, the nucleic acid-lipid complexes of Lee et al. do not comprise a nucleic acid fully encapsulated in a liposome. These arguments are not found to be persuasive. As previously pointed out, it is unclear to the examiner as to how one can come to the conclusion that a complex of nucleic acid (anionic)- polylysine (cationic) complex does not cross lipid membrane, just because anionic DNA does not cross lipid membrane since the charges are neutralized in a complex. Secondly, these arguments appear to be speculative. Thirdly, Figure 1 in Lee clearly shows the encapsulation of the complex

and Example 1 of Lee clearly states, "Preparation of liposome-based lipidic vector which **encapsulates DNA**".

3. Claims 1-6, 8,12-13, 15-17, 21-22, 28, 32-37, 39, 43-45,49, 55, 57 and 59 are rejected under 35 U.S.C. 102(a) as being anticipated by Martin (5,891,468).

Martin discloses compositions containing condensed nucleic acid preparations encapsulated within the liposomes for transfection. The liposomes contain PE, lipid derivatized with PEG (1-20 mole percent). The sizes of the liposomes range from 100-150 nm (col. 7, lines 14-27, col. 8, lines 18-37, col. 16, line 14 through 65, col. 21, lines 4-21, Examples 9 and 11).

Applicant's arguments and declaration have been fully considered, but are not persuasive. Applicant based on Dr. Mac Lachlan's declaration once again argues that Martin discloses complexes formed by mixing preformed liposomes with plasmid-histone complexes and thus, Martin does not describe nucleic acid-histone complexes fully encapsulated in a liposome (declaration # 10). Applicant is incorrect in stating that Martin's complexes are not encapsulated. First of all on col. 21, lines 18-21 Martin clearly states that a solution of the condensed nucleic acid molecules is used to rehydrate the dry lipid film to form liposomes ***with the condensed nucleic acid in entrapped form.*** Furthermore, Martin in Example 11 on col. 31 shows how to prepare the entrapped, condensed plasmid molecules. Applicant's arguments based on the experiments conducted by Dr. Mac Lachlan that the dehydration-rehydration-extrusion methods described in Martin cannot be used to encapsulate nucleic acids are not persuasive since these experiments appeared to have been done with nucleic acids by

themselves and not in a complex form with the condensing agent. Applicant's arguments based on the experiments set forth in Exhibit B are not persuasive since as admitted by applicant himself, 12 to 15 percent of the input nucleic acid was inaccessible to Picogreen due to its association with or ***incorporation into*** > 10,000 nm multilamellar vesicles; since the instant independent claim does not recite any percentages of encapsulation, the reference still meets the requirements of instant claims. Even assuming that dehydration-rehydration does not result in the encapsulation of the complex, as pointed out above, example 11 of Martin clearly shows encapsulation of the complex in the liposomes.

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-8, 12-13, 15-17, 21-22, 32-39, 43-45, 49, 55, 57 and 59 are rejected under 35 U.S.C. 102(a) as being anticipated by Lee (J. Boil. Chem., 1996).

Lee discloses compositions containing condensed nucleic acid preparations encapsulated within the liposomes for transfection. The liposomes contain DOPE/PS and PEG-PE. The condensing agent is polylysine, (abstract and the whole publication). As stated above, although Lee does not specifically state the molecular weight of PEG, PEG-lipid complex in Lee is prepared according to the method of by Lee's previous work wherein PEG 2000 was used.

Applicant's arguments are fully considered, but are not found to be persuasive. Applicant's arguments to this rejection are similar to those put forward for the above rejection over Lee (777) and hence the same response is applicable.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 11-14, 26-28, 30-31, 42, 52-53, 56, 58 and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee (5,908,777) or Lee (J. Biol. Chem) cited above.

The teachings of Lee (777), Lee (JBC) have been discussed above. What are lacking in Lee are the teachings of the diameters of the complex (condensing agent and the nucleic acid). Since this parameter depends upon the amount of the nucleic acid to be encapsulated, in the absence of showing of unexpected results, it is deemed obvious to one of ordinary skill in the art to manipulate the teachings of Lee with the expectation of obtaining the best possible results. Similarly, instant liposome sizes are deemed to be obvious in view of Lee's teachings on col. 8, line 54 et seq., which the size of the DNA containing liposomes depends on the charge between the complex and the anionic liposomes. Lee also lacks the teachings of the claimed lipid: nucleic acid ratios. This parameter once again is deemed to obvious to one of ordinary skill in the art in view of the relationship between the charge of the complex, the sizes of the liposomes and also because of the nature of the transfection to be carried out. Lee does not teach the

addition of the condensing agent in stages or the addition of two condensing agents. However, since the purpose of the condensing agent is to condense the nucleic acid molecule and to protect the nucleic acid from degradation, in the absence of showing unexpected results, such a manipulation is deemed to be within the skill of the art.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues that neither Lee et al nor Lee et al 2 disclose or even suggest the presently claimed liposomes encapsulating a nucleic acid-condensing agent complex and in the absence of such a teaching or suggestion, the compositions and methods of the presently claimed invention are nonobvious. As discussed above, applicant is incorrect in stating that Lee does not teach instant encapsulated complexes. The rejection is maintained.

7. Claims 17-22, 28-29, 45-48, 53-54, 60 and 63-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee 5,908,777 or Lee, J. Bio. Chem., or Martin (5,891,468) cited above, further in view of Holland (5,885,613).

The teachings of Lee, and Martin have been discussed above. What is lacking in these references is the teaching of PEG ceramide as the bilayer-stabilizing component. What are also lacking in these references are the explicit teachings of the molecular weights of PEG and PEG-lipid amounts in molar percentages.

Holland while disclosing liposomal compositions for the delivery of nucleic acids teaches that PEG when attached to phosphatidylethanolamine (PE) or ceramide (C 14-C20 ceramides) stabilizes the bilayer. The Molecular weight range of PEG is 200-10,000 and the amount of the PEG-lipid is in the range of 0.05 to 30 mole percent

(abstract, col. 8, line 60 through col. 9, line 57, col. 24, line 4 through col. 25, line 46 and claims).

The use of PEG-ceramide as the PEG lipid instead of PEG-PE would have been obvious to one of ordinary skill in the art since Holland teaches the effectiveness of both PEG-PE and PEG-ceramide in liposome compositions used in the delivery of nucleic acids. Choosing the appropriate amounts of PEG-lipid and PEG with desired molecular weight with a reasonable expectation of success would have been obvious to one of ordinary skill in the art since Holland teaches manipulations with these parameters.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments once again are based on the lack of teachings of encapsulated complexes in Lee, Lee 2 and Martin. These have been addressed above. Applicant's arguments that the teachings of Holland are clearly directed to forming nucleic acid-cationic liposome complexes, which are structurally and functionally different from the presently claimed liposomes, and as explained by Dr. Mac Lachlan, the dehydration-rehydration-extrusion methods set forth in Holland cannot be used to encapsulate a nucleic acid in a liposomes are not persuasive. Holland is combined for its teachings of the use of PEG-ceramide or PEG-PE in the preparation of fusogenic liposomes and applicant has not shown any unexpected results obtained by substituting PEG-PE with PEG-ceramide of Holland. With regard to the dehydration-rehydration taught by Holland: - the examiner has already addressed arguments based on dehydration-rehydration above.

8. Claims 8-10, 23-25, 39-40, 50-51 and 61are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee (5,908,777), or Lee (J. Biol. Chem), or Martin (5,891,468) cited above, further in view of Lisziewicz (6,420,176).

The teachings of Lee or Martin have been discussed above. What are lacking in these references are the teachings of the use of polyethylenimine as the polycation or the condensing agent.

Lisziewicz while disclosing compositions for delivering DNA into cells teaches that the cationic polymer, polyethylenimine (PEI 25 kD) is effective in binding to DNA and makes a complex and this complex can enter into endosomes of the skin's antigen presenting cells, Langerhans cells, via asialoglycoprotein receptor-mediated endocytosis (abstract, col. 10, line 24 et seq., and claims).

The use of PEI as the polycation in the teachings of Lee or Martin with a reasonable expectation of success since Lisziewicz teaches the ability of this polycation to bind to DNA and effectively enter into endosomes of the skin's antigen presenting cells, Langerhans cells, via asialoglycoprotein receptor-mediated endocytosis.

Applicant's arguments have been fully considered, but are not found to be persuasive. The arguments regarding Lee, and Martin have already been addressed above. Applicant once again argues that Lisziewicz does not remedy the defect in any of the cited references and that the reference teaches away from the use of PEI because Lisziewicz compares PEI and PEI-mannose as a condensing agent and demonstrates that relative to PEI mannose, PEI is more toxic, requires more DNA to neutralize and is less efficient for transfection. These arguments are not persuasive

since the comparison made by Lisziewicz is between PEI and PEI-mannose and that too while using a specific cell population and not a comparison between PEI and other condensing agents taught by the primary references. Secondly, Lisziewicz clearly states on col. 10, line 24 that PEI is the preferred embodiment. Thirdly, if PEI is toxic and in efficient, then one would expect the same properties even in instant invention compared to PEI-mannose.

9. Claims 65-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee 5,908,777 or Lee, J. Bio. Chem., or Martin (5,891,468) cited above, in combination with WO 98/20857 of record.

The teachings of Lee 777, JBC and Martin have been discussed above. What is lacking in these references is the method of preparation of liposomes by reverse phase evaporation method (ethanol injection) or using detergent dialysis.

As pointed out in the previous action, WO 98 discloses liposomal formulations containing nucleic acid complexes and a method of transfection. The nucleic acid is reacted with an organic polycation (spermidine, spermine) to produce a condensed nucleic acid. The composition is further stabilized by the addition of a hydrophilic polymer (PEG). The phospholipids taught by WO include phosphatidic acid, phosphatidylcholine. The liposomes are prepared by using the standard methods of liposomes including detergent dialysis and reverse phase evaporation (abstract, pages 3-4, 7-9, 12, 16-17, 22-25, Examples and claims).

The preparation of liposomes of Lee or Martin by reverse phase evaporation and detergent dialysis methods would have been obvious to one of ordinary skill in the art

with a reasonable expectation of success, since these are art known methods as taught by WO.

Applicant's arguments have been fully considered, but are not found to be persuasive. The arguments regarding Lee, and Martin have been addressed above. Applicant's argument that WO does not remedy the defect in the primary references since it discloses nucleic acid-lipid complexes formed by mixing preformed liposomes with nucleic acids which leads to formation of lipocomplexes. These arguments are not found to be persuasive. WO is combined to show the art known knowledge of the preparation of liposomes using reverse phase evaporation and detergent dialysis methods and one of ordinary skill in the art would be motivated to use a solution of the complex of nucleic acid-condensing agent before the formation of the liposomes as performed by Martin. Furthermore, an artisan would be aware that by complexing nucleic acids with condensing agents would result in a complex in which the charges of the nucleic acids are neutralized and therefore, the complexes will not behave the same way as nucleic acids.

The reference of Thierry (6,110490) is cited of interest (see col. 15, lines 1-11; col. 16, lines 7-12; col. 25, lines 37-39).

10. This is a RCE of applicant's earlier Application No. 09/744,103. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL**

even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK